fused to protein and/or peptide subunits. Importantly, genetic fusion produces a continuous polypeptide chain of the subunit in which the first binding moieties are incorporated. Accordingly, all corresponding subunits of the apoferritin where a first binding moiety has been genetically fused are identical to one another, i.e., the binding moieties are each located at the same place in the subunit's polypeptide chain. See the Rule 132 Declaration filed April 3, 2009 ("the Lamminmäki Declaration"), particularly paragraph Nos. 9-12. An essential advantage of the present invention is that the ferritin protein can be tailored using a fusion protein which incorporates all essential elements and which self-assembles into a nanoparticle particularly suitable for ligand binding bioaffinity assays.

The cited combination of references fails to raise a prima facie case of obviousness against the claimed nanoparticle because one of ordinary skill in the art would not combine the references as proposed by the Examiner. In this regard, the Patent Office concedes Kameda et al. fails to disclose the genetically fused first binding moiety of the claimed recombinant nanoparticle (Official Action, page 3, last sentence). Instead, Kameda et al. chemically binds its binding moieties to ferritin subunits, which

produces random distribution of the binding moieties on the polypeptide chain. See paragraph No. 10 of the Lamminmäki Declaration.

The Patent Office's reliance on Willner et al. to show genetically fused proteins is misplaced. First, one of ordinary skill would not combine Kameda et al. with Willner et al. because Willner et al. is non-analogous art. Relevant art is (1) prior art within the field of the inventor's endeavor, regardless of the problem addressed and (2) prior art in other arts which are reasonably pertinent to the particular problem with which the inventor was involved. In re Clay, 966 F.2d 656, 658-59, 23 USPQ2d 1058, 1060 (Fed. Cir. 1992).

Willner et al. is non-analogous art which discloses the detection of small molecules using a piezoelectric sensor. This reference is not directed to the inventors' field of endeavor (apoferritin nanoparticles) nor reasonably pertinent to the problem with which the inventors were involved (heterogenous reaction products). Accordingly, one of ordinary skill in the art would not consider Willner et al., much less combine it with Kameda et al.

Second, even assuming Willner et al. is available against the claims, one of ordinary skill in the art is given no motivation or

suggestion to modify Kameda et al.'s chemically-fused ferritin particle. The Official Action points to two sentences in Willner et al. (Col. 9, lines 46-48) which suggest a binding domain may be conjugated or fused to a macromolecular moiety, and that such conjugation or fusion "may be achieved, as known, by chemical binding, by genetic engineering techniques, etc." However, there is no disclosure of the relative advantages or disadvantages of the two techniques in Willner et al., *and no suggestion to prepare recombinant apoferritin particles from genetically fused binding moieties.*

The Patent Office argument that chemical conjugation and genetic fusion are "functionally equivalent attachment techniques" is incorrect, at least with respect to the claimed ferritin nanoparticle. Ferritin nanoparticles produced by chemical conjugation of protein subunits comprise a heterogeneous reaction product in which chemical conjugation can occur in different positions in the ferritin sub-unit; in contrast, ferritin nanoparticles produced by genetic fusion comprise a homogenous reaction product which exhibits a constant orientation/conformation of binding moieties. See paragraph Nos. 6-8 of the Lamminmäki Declaration.

Willner et al. fails to disclose or suggest the production of a recombinant apoferritin particle. Instead, Willner et al. merely shows formation of a fusion protein through engineering techniques was known. Taken to its logical conclusion, the Patent Office argument would hold *all* recombinant products *per se* obvious once the art of genetic engineering was discovered, regardless of the structural distinctions and properties of the specific recombinant product. In this case, the claimed recombinant nanoparticle comprises all essential characteristics required for use in a ligand binding bioaffinity assay because characteristics not intrinsic to ferritin *per se* have been introduced via genetic fusion into the ferritin protein.

It is respectfully submitted the Patent Office has improperly employed hindsight to pick and choose an isolated disclosure in Willner et al. and combine it with Kameda et al., despite the absence of any motivation or suggestion within the prior art to prepare recombinant apoferritin particles from genetically fused binding moieties. Reconsideration and withdrawal of the obviousness rejection of claims 26, 27, 29 and 36-38 over Kameda et al. in view of Willner et al. are respectfully requested.

The 35 U.S.C. § 103(a) rejection of claim 30 over Kameda et al. and Willner et al., further in view of U.S. Patent No. 6,713,274 to Bertozzi et al., is also traversed. As discussed above, the claimed nanoparticle is a recombinant apoferritin particle, a recombinant Dpr protein particle or a recombinant Dps protein particle, in which at least a first binding moiety has been genetically fused to protein and/or peptide subunits. A structural feature of the claimed nanoparticle is that all corresponding subunits of the apoferritin where a first binding moiety has been genetically fused are identical to one another.

The cited combination of references fails to raise a prima facie case of obviousness against claim 30 because one of ordinary skill in the art would not combine the references as suggested by the Patent Office.

The deficiencies of Kameda et al. and Willner et al., discussed above, are not remedied by the additional disclosure of Bertozzi et al., which is cited to show fluorescein, luciferase and $^{124}$Eu may be used as a detectable label for detection of antibody binding.

Bertozzi et al., like Willner et al., fails to disclose or suggest modifying Kameda et al.'s ferritin nanoparticle by

preparing it using genetic fusion. Reconsideration and withdrawal of the obviousness rejection of claim 30 over Kameda et al., Willner et al. and Bertozzi et al. are earnestly requested.

The 35 U.S.C. § 103(a) rejection of claim 31 over Kameda et al. and Willner et al., further in view of U.S. Patent Publication 2003/0124586 to Griffiths et al., is traversed. The claimed nanoparticle is a recombinant apoferritin particle, a recombinant Dpr protein particle or a recombinant Dps protein particle, in which at least a first binding moiety has been genetically fused to protein and/or peptide subunits. A structural feature of the claimed recombinant nanoparticle is that all corresponding subunits of the apoferritin where a first binding moiety has been genetically fused are identical to one another.

The cited combination of references fails to raise a prima facie case of obviousness because none of the cited references disclose or suggest the genetically fused, uniform subunit feature of the claimed nanoparticle. The deficiencies of Kameda et al. and Willner et al., discussed above, are not remedied by the additional disclosure of Griffiths et al., which is cited to show a third binding moiety. However, Griffiths et al. provides no motivation to modify Kameda et al.'s ferritin nanoparticle by preparing it

from binding moieties which have been genetically fused to protein and/or peptide subunits. Reconsideration and withdrawal of the obviousness rejection of claim 31 are respectfully requested.

The 35 U.S.C. § 103(a) rejection of claims 28 and 32 over Kameda et al. and Willner et al., further in view of U.S. Patent No. 6,599,331 to Chandler et al., is traversed. The claimed nanoparticle is a recombinant apoferritin particle, a recombinant Dpr protein particle or a recombinant Dps protein particle, in which at least a first binding moiety has been genetically fused to protein and/or peptide subunits. A structural feature of the claimed recombinant nanoparticle is that all corresponding subunits of the apoferritin where a first binding moiety has been genetically fused are identical to one another.

The cited combination of references fails to raise a prima facie case of obviousness against the claimed nanoparticle because none of the cited references disclose or suggest the genetically fused, uniform subunit feature of the claimed nanoparticle. The deficiencies of Kameda et al. and Willner et al., discussed above, are not remedied by the additional disclosure of Chandler et al., which is cited to show the use of protein A as a binding moiety. However, Chandler et al. provides no motivation to modify Kameda et

al.'s ferritin nanoparticle by preparing it using genetic fusion. Reconsideration and withdrawal of the obviousness rejection of claims 28 and 32 are respectfully requested.

The 35 U.S.C. § 103(a) rejection of claims 33, 35 and 36 over Kameda et al. and Willner et al. in view of U.S. Patent No. 6,537,760 to Bergmann et al. is traversed. The claimed nanoparticle is a recombinant apoferritin particle, a recombinant Dpr protein particle or a recombinant Dps protein particle, in which at least a first binding moiety has been genetically fused to protein and/or peptide subunits. A structural feature of the claimed recombinant nanoparticle is that all corresponding subunits of the apoferritin where a first binding moiety has been genetically fused are identical to one another.

The cited combination of references fails to raise a prima facie case of obviousness against the claimed nanoparticle because none of the cited references disclose or suggest the genetically fused, uniform subunit feature of the claimed nanoparticle. The deficiencies of Kameda et al. and Willner et al., discussed above, are not remedied by the additional disclosure of Bergmann et al., which discloses a competitive receptor binding assay for detecting TSH-receptor auto-antibodies. Bergmann et al. does not provide one

of ordinary skill in the art with any suggestion or motivation to prepare Kameda et al.'s nanoparticle by genetically fusing a first binding moiety to a protein and/or peptide sub-unit. Reconsideration and withdrawal of the obviousness rejection of claims 33, 35 and 36 over Kameda et al., Willner et al. and Bergmann et al. are respectfully requested.

The 35 U.S.C. § 103(a) rejection of claim 34 over Kameda et al. and Willner et al., further in view of U.S. Patent Publication No. US 2003/0077578 to Oon et al., is traversed. The claimed nanoparticle is a recombinant apoferritin particle, a recombinant Dpr protein particle or a recombinant Dps protein particle, in which at least a first binding moiety has been genetically fused to protein and/or peptide subunits. A structural feature of the claimed recombinant nanoparticle is that all corresponding subunits of the apoferritin where a first binding moiety has been genetically fused are identical to one another.

The cited combination of references fails to raise a prima facie case of obviousness against the claimed nanoparticle because none of the cited references disclose or suggest the genetically fused, uniform subunit feature of the claimed nanoparticle. The deficiencies of Kameda et al. and Willner et al., discussed above,

are not remedied by the additional disclosure of Oon et al., which discloses a nucleic acid based assay for detection of a virus pathogen such as hepatitis B virus. One of ordinary skill in the art is given no suggestion or motivation to prepare Kameda et al.'s nanoparticle by genetically fusing a first binding moiety to a protein and/or peptide sub-unit from Oon et al. Reconsideration and withdrawal of the obviousness rejection of claim 34 are respectfully requested.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of all rejections of claims 26-38, and issuance of a Notice of Allowance directed to those claims, are earnestly requested. The Examiner is urged to telephone the undersigned should she believe any further action is required for allowance.

The fee for the extension of time is being paid electronically today. It is not believed any additional fee is required for entry and consideration of this Request for Reconsideration.

Nevertheless, the Commissioner is authorized to charge Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

/James C. Lydon/

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Enclosure:
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